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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/748,177	12/31/2003	Andrew P. Levy	P-7339-US	7660

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EXAMINER

GOLDBERG, JEANINE ANNE

ART UNIT PAPER NUMBER

1634

DATE MAILED: 03/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/748,177

Applicant(s)

LEVY, ANDREW P.

Examiner

Jeanine A. Goldberg

Art Unit

1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 November 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-29 is/are pending in the application.
- 4a) Of the above claim(s) 6-11, 20-25 and 29 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5, 12-19 and 26-28 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. This action is in response to the papers filed November 28, 2005. Currently, claims 1-29 are pending. Claims 6-11, 20-25, 29 have been withdrawn as drawn to non-elected subject matter.

Election/Restrictions

2. Applicant's election without traverse of Group II, Claims 1-5, 12-19, 26-28 in the paper filed November 28, 2005 is acknowledged.

The response to the restriction is made with traverse. The response asserts that upon allowance of the linking claims, the restriction requirement as to the linked inventions shall be withdrawn. This argument has been thoroughly reviewed and deemed persuasive. Upon allowance of a linking claim, the withdrawn claims which are linked by the linking claim will be rejoined.

Claims 6-11, 20-25, 29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement.

The requirement is still deemed proper and is therefore made FINAL.

This application contains claims 6-11, 20-25, 29 drawn to an invention nonelected with traverse in the paper filed November 28, 2005. A complete reply to the

final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Priority

3. This application claims priority to numerous US Patent applications.
Applicant is required to update the first line of the specification to reflect the status of each of these applications prior to allowance.

Information Disclosure Statement

4. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Pages 48-54 contain a list of references which have not been considered as they have not been provided or cited on a 1449.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

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art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-5, 12-19, 26-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of determining a potential of a diabetic patient to benefit from vitamin E therapy for treatment of CV death or MI wherein the benefit from said vitamin E therapy to a patient having a haptoglobin 2-2 phenotype is greater compared to patients having haptoglobin 1-2 phenotype or 1-1 phenotype, does not reasonably provide enablement for a method of determining a potential of a diabetic patient to benefit from any anti oxidant therapy for treatment of any vascular complication wherein the benefit. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

The claims are drawn to a method of determining a potential of a diabetic patient to benefit from anti oxidant therapy for treatment of a vascular complication by

determining a haplotype phenotype of the diabetic patient and thereby determining the potential of the diabetic patient to benefit from said anti-oxidant therapy.

The invention is in a class of invention which the CAFC has characterized as “the unpredictable arts such as chemistry and biology.” *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the art

The art teaches the effect of vitamin therapy on the progression of coronary artery atherosclerosis varies by haptoglobin type in postmenopausal women (Levy et al. *Diabetes Care*, Vol. 27, No. 4, pages 925-930, April 2004). Levy teaches that changes in the MLD as a function of haptoglobin phenotype and vitamin therapy were analyzed. The analysis of changes in LDL and HDL levels with and without vitamin therapy were analyzed in diabetic patients. The LDL levels in Diabetic patients was not significantly different between vitamin and placebo treated (see Table 4).

The art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (*Genetics in Medicine*. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and

disease susceptibility.

Additionally, Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

Guidance in the Specification and Working Examples

The specification provides no evidence that the broad scope of the claims are enabled. The specification has analyzed vitamin E and Ramipril which are deemed to be two particular anti-oxidant therapies. The specification teaches there is a 100% concordance between the haptoglobin phenotype as determined from plasma and the haptoglobin genotype as determined from genomic DNA by the PCR. As seen in Table 5 of the instant specification (page 45), the analysis based on DM patients only did not provide a statistically significant result for Hp 2-2 phenotype for stroke when treated with vitamin E. Table 6 illustrates that in diabetic patients the Hp 2-2 phenotype is not associated with CV death, MI or Stroke. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention as broadly as claimed.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied.

The claims are broadly drawn to any vascular complication, however, the specification fails to provide a significant association between CV, MI or stroke. Given the guidance in the instant specification it is clear that the skilled artisan would not be able to use the presence of the Hp 2-2 phenotype as indicative of CV, MI or stroke. The non-significant p-values provided for the analysis in the specification do not support a method for determining a potential of a diabetic patient to benefit from oxidant therapy. While the skilled artisan could provide additional experimentation to determine whether a subgroup of the population, or another population may have an association between hp 2-2 phenotype and all vascular diseases, the results are unpredictable, since three of the four complications studied did not yield positive associations.

Furthermore, given the analysis in the specification of vitamin E and Ramipril, there is no predictable correlation between Hp 2-2 phenotype and greater benefit for anti oxidant therapy. Diabetic patients with CV death and MI appear to be significantly associated with vitamin E. However, diabetic patients provided Vitamin E showed no association with stroke. The association pattern for Ramipril is different. CV death, MI and Stroke each do not appear to be significantly associated with Hp 2-2 phenotype in diabetics. Based upon the different patterns, the administration of one anti-oxidant therapy would not be indicative of each other anti-oxidant therapy. For example, since Vitamin E and Ramipril each have different associations, it would unpredictable whether Vitamin C, for example, would be associated with anti oxidant therapy benefits. The specification does not provide any analysis for diabetic retinopathy, nephropathy or neuropathy, for example. Therefore, it would be unpredictable whether either Vitamin E, Vitamin C or Ramipril would be associated with Hp 2-2 phenotype and benefits from anti-oxidant therapy.

This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the specification and the art do not provide a reliable association between anti oxidant therapies and benefits to vascular complications in diabetic patients. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized problems for association studies. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Conclusion

6. No claims allowable.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.



Jeanine Goldberg

Primary Examiner

March 1, 2006